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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/226,044	01/05/1999	ALLAN S. HOFFMAN	UWS-102	1587

23579 7590 07/01/2003

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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	30

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/226,044	Hoffman
Examiner	**Art Unit**
Gollamudi Kishore	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 17, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *34-37, 39, 41-52, 55-77, 79, 81-90, 101, and 102* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *34-37, 39, 41-52, 55-77, 79, 81-90, 101, and 102* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request for the extension of time, amendment and the declaration filed on 3-17-03 are acknowledged.

Claims included in the prosecution are 34-37, 39, 41-52, 55-77, 79, 81-90 and 101-102.

Claim Rejections - 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless --**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

2. Claims 34-35, 37-38, 41-43, 47-48, 50, 66, 68, 70-75, 77, 79, 81 and 83-86 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/14142.

WO discloses a method of drug delivery using polymeric carriers. The drugs include anti-cancer drugs and photoactivatable drugs. The polymeric compounds include copolymers of various acrylamides, acrylic acid, methacrylic acid, polysaccharides and polyamino acids; the compositions further contain a targeting agent such as an antibody (note the abstract, pages 6-7, 10-11, 15, 18, Examples and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that WO teaches a composition that enters the cell through

pinocytosis and that the reference fails to describe a composition that is effective in disrupting the lysosomal membrane. This argument is not found to be persuasive since the instant claims are drawn to a method of delivering a therapeutic or diagnostic agent to a cell and the reference teaches a method of drug delivery using the copolymers of acrylic acid, methacrylic acid and the mechanism by which they act has no patentable significance. With regard to arguments based on the declaration of Patrick Stayton, the examiner points out that first of all, a declaration cannot overcome a 102 rejection and secondly, the reference teaches copolymers and the declaration is based on polyacrylic acid and poly(methylacrylic acids which are homopolymers. Instant claim language allows both homo and copolymers.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 34-37, 39, 41-43, 47-50, , 57-59, 64-77, 79, 81 and 83-86 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/09068 of record.

WO 09068 teaches stimuli-responsive polymer systems for drug delivery (note the abstract and the entire patent). The composition contains a the polymer chain which is responsive to changes in pH, temperature, light or other stimuli and a molecule such as a hormone or an enzyme (abstract, pages 10-27, in particular pages 17-23; 36 and 50-54).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant while agreeing that the reference describes delivery of a drug into a

cell, within an endosome, where the drug is released inside the liposome, where the linkage of the polymer to the drug is labile, argue that the reference fails to describe a composition that is effective in disrupting the lysosomal membrane, or a method in which lysosomal membrane is disrupted. This argument is confusing. First of all, as applicants themselves recognize the composition enters the endosomes implying that the endosomal membrane is disrupted to some extent allowing the composition to enter. Instant claims just recite 'disrupting the endosomal membrane' without reciting the degree of disruption. The claims do not also recite lysosomes. Therefore, the reference meets the requirements of instant claims. With regard to the arguments based on the declaration, the examiner once again points out that a declaration cannot overcome a 102 rejection. The argument that the declaration shows that polyacrylic acid and poly(methylacrylic acid) are ineffective in hemolysis at the pH found in endosomes are not found to be persuasive since the claims do not recite hemolysis and the very fact that the reference teaches at the location pointed out by applicants themselves (pages 53 and 54), the reference teaches that the polymer-drug complex is labile to a pH of approximately 4 or 5 which according to the reference is the pH of the endosome.

Claim Rejections - 35 U.S.C. § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

5. Claims 34-37, 39, 41-52, 55-77, 79, 81-90 and 101-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/14142 or WO 97/09068.

The teachings of WO 93 and WO 97 have been discussed above. These references teach copolymers obtained from the monomers of acrylic acid and methacrylic acid. They do not teach ethylacrylic acid, propylacrylic acid and butylacrylic acid. However, since these are homologues of methacrylic acid, it is deemed obvious to one of ordinary skill in the art to the claimed monomers since homologues are expected to behave the same way. The references do not explicitly teach the behavior of the polymers with respect to the pH changes. However, since the references teach the same polymers, it would have been obvious to one of ordinary skill in the art that they would behave the same way when the pH is changed. WO 93 and 97 do not teach the claimed active agents such as toxins; however, it would have been obvious to one of ordinary skill in the art to use any active agent including the claimed toxins since the principle of release of the active agent in the cytosol is the same irrespective of the active agent.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants points out the results in the declaration and argue that the declaration demonstrates the pH behavior of polyacrylic acid, and poly(methylacrylic acid) is dramatically different from that of (PEAA) poly(ethylacrylic acid) and (PPAA) poly(propylacrylic acid). This argument is not found to be persuasive since a careful evaluation of the Figure 2 showing the hemolysis shows that the pH profile of PPAA itself is different from that of PEAA. PPAA appears to cause hemolysis at pH range above 5.8 (according to WO 97/09068 the pH range of endosome is 4 and 5 as discussed above), whereas PEAA causes the hemolysis within pH 6.2. In other words, it is unclear to the examiner how this can be correlated to the claimed pH values in instant clams. Furthermore, instant claims recite hydrophilic nature and hydrophobic nature of the polycarboxylic acid at the claimed pH ranges and the data in the declaration is not reflective of that. In addition, the data is not commensurate the scope of the claims with respect to the broad expression, 'polycarboxylic acid'.

6. Claims 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/14142 or WO 97/09068, further in view of Berg (5,876,989).

As pointed out above, WO 93 discloses a method of drug delivery using polymeric carriers. The drugs include anti-cancer drugs and photoactivatable drugs. The polymeric compounds include copolymers of various acrylamides, acrylic acid, methacylic acid, polysaccharides and polyamino acids; the compositions further contain a targeting

agent such as an antibody (note the abstract, pages 6-7, 10-11, 15, 18, Examples and claims).

As also pointed out above, WO 97 teaches stimuli-responsive polymer systems for drug delivery (note the abstract and the entire patent). The composition contains a the polymer chain which is responsive to changes in pH, temperature, light or other stimuli and a molecule such as a hormone or an enzyme (abstract, pages 10-27, in particular pages 17-23; 36 and 50-54).

What is lacking in these references is the teaching that the active agent to be a toxin such as those claimed in instant claims.

Berg cited above discloses compositions and a method of releasing molecules into the cytosol. The molecules are taken up endosomes and released into cytosol by an external stimulus such as light activation of photosensitive compounds. The compositions contain a carrier, a toxin (gelonin) or nucleic acid and a photosensitive agent (note the abstract, columns 4-5, Examples and claims).

In essence WO publications and Berg deal with the same concept: that is the compositions entering the endosomes and subsequently released in the cytosol. Therefore, it would have been obvious to use any active agent including the claimed toxins in WO 93 or 97 with the expectation of similar release sine Berg teaches that toxins such as gelonin can be administered using the same principle.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that Berg fails to teach or suggest a composition or method that includes a polymer carrier. The examiner agrees, but points out that Berg is combined for its teachings of the delivery of toxins based on the same principle, that is the delivery to the endosomes.

7. Claim 36 is are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/14142 or WO 97/09068 in view of Shapland (5,807,306) of record.

The teachings of WO 93 and 97 have been discussed above. What is lacking in these references is the teaching of the stimulus being ultrasound.

Shapland while disclosing drug delivery systems teaches that the drug could be released internally using ultrasound or iontophoresis (note the abstract, column 16 and claims).

The use of ultrasound as the external stimulus in the teachings of WO 93 or 97 would have been obvious to one of ordinary skill in the art since the reference of Shapland teaches that release of the drug could be accomplished by using an external stimulus such as ultra sound or iontophoresis. One of ordinary skill in the art would be motivated to used ultrasound with the expectation of the drugs in WO 93 or 97.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that none of the references teach the disrupting the endosomal membrane and that they fail to teach a composition that includes a

polycarboxylic acid polymer that is hydrophilic at the pH values claimed; these arguments have already been addressed above.

8. Claims 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/14142 or WO 97/09068 in view of Anderson (Bioconjugate Chemistry, 4, 1993, pp. 10-18) of record.

The teachings of WO 93 and 97 have been discussed above. In essence these references teach the polymer-drug combination and also the attachment of peptides the polymers. The composition in these references also respond to the external stimuli, thus releasing the drug in the cytosol. What is lacking in these references is the teaching that the polymers be conjugated to GALA peptide.

Anderson teaches that GALA peptides enhance the internalization of antibodies in tumor cells when the antibodies are attached to GALA peptides (note the abstract). It would have been obvious to one of ordinary skill in the art to attach GALA to the polymers of WO 93 and 93 since such an attachment would enhance the internalization of the complex in the tumor cells and release the drug in the cytosol with the subsequent application of the external stimuli.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants' arguments are similar to those above and therefore, the same response is applicable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600